Scientific paper

New Benzo- and Thieno-fused Spirolactams

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Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

A short and efficient approach leading to new spiro compounds joining benzo- and thieno-fused lactams and piperidine is presented. Various derivatives were prepared by alkylation of 1-methylpiperidinecarboxylates, cyclization to spiro-ketones, and subsequent Beckmann rearrangement of the corresponding oximes.

Keywords: Spiro compounds, Beckmann rearrangement, oximes, lithiation, ring extension

1. Introduction

Spiro compounds are present in a multitude of natural products and pharmaceutical compounds.[1] The most frequently applied spiro-compounds in context of pharmaceuticals are the diuretic spironolactone[2] and the antibiotic griseofulvin[3] (Scheme 1) but ongoing research in this field reveals constantly new structures with promising activities.[4] Our group has been active since many years in this area developing synthetic strategies in particular for a series of thieno-fused carbocyclic spiranes of type **I**.[5] Later, additional heterocyclic rings were incorporated, e. g. type **II**[6a] and application of directed lithiation strategies led to structures of type **III**[6b–d] (Scheme 1).

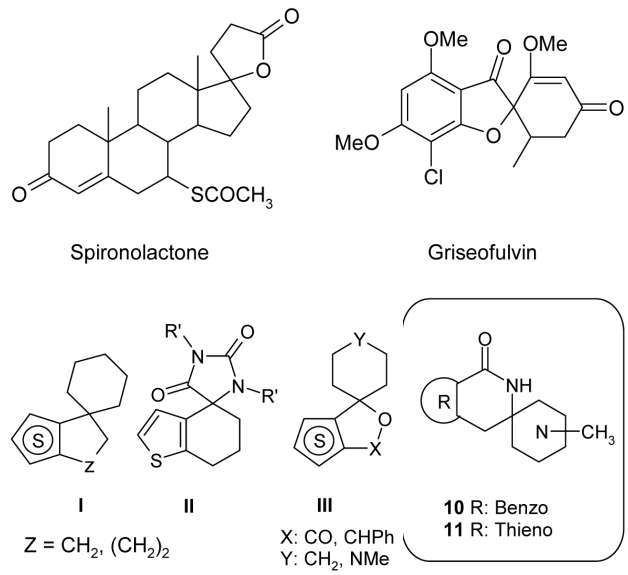
In the present work we extended our efforts to further variations of the center ring system by introducing a lactam moiety with the aim of preparing target molecules of the general type **10** and **11** with different positions of the nitrogen atom within the piperidine part.

2. Results and Discussion

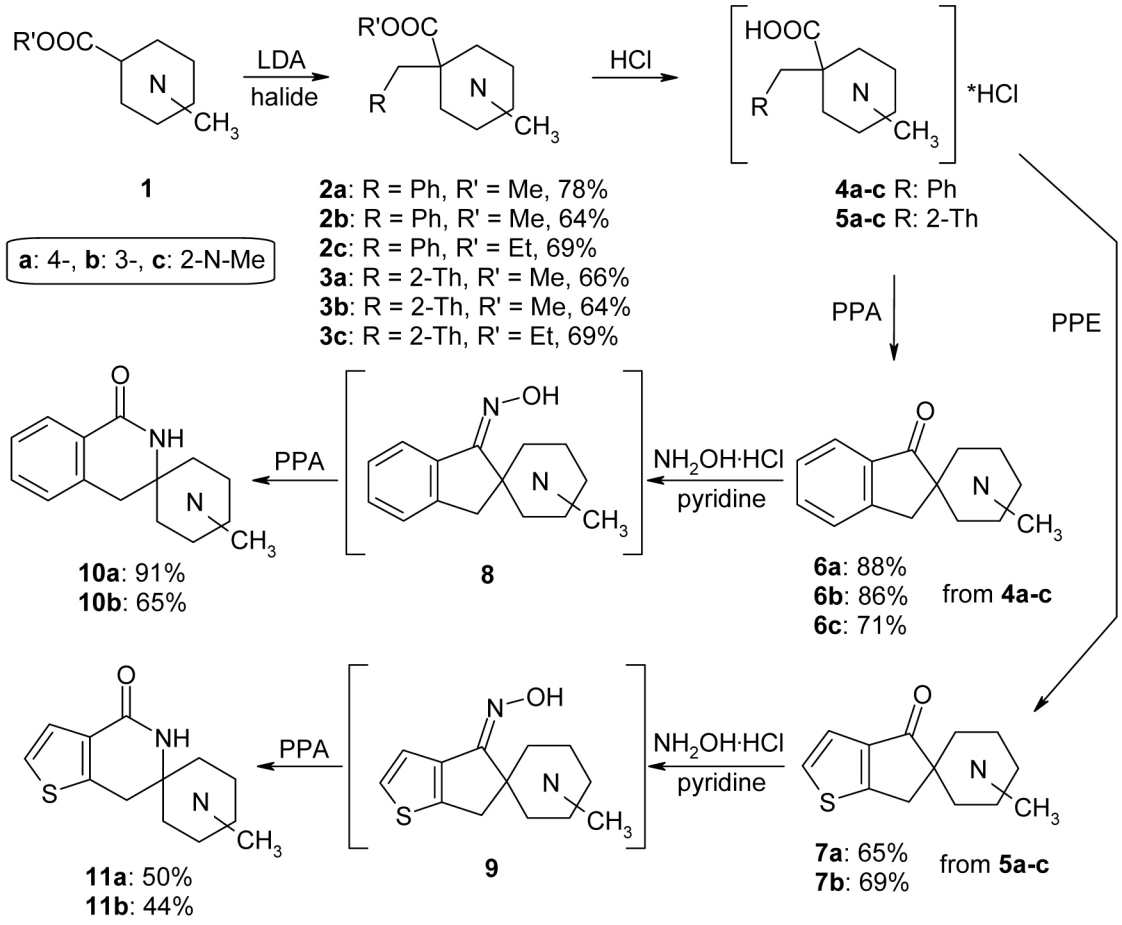
Retrosynthetic analysis of the target compounds suggested an appealing strategy with a ring expansion reaction as the last step. Access to the necessary intermediates was envisaged via an intramolecular Friedel-Crafts acylation of piperidinecarboxylates of type **2** and **3** leading back to easily available starting materials **1** (Scheme 2).

The 1-methylpiperidinecaboxylates **1a,b** were prepared according to a literature protocol[7] whereas **1c** was commercially available.

According to our strategy, alkylation of deprotonated 1-methylpiperidinecarboxylates **1a-c**, with benzyl

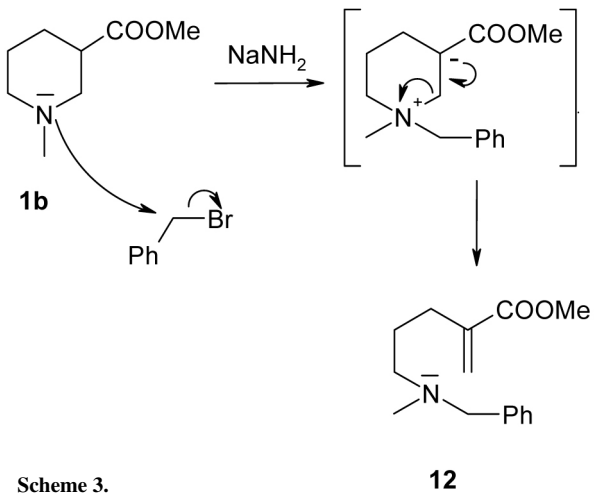


Scheme 1.



Scheme 2. Reaction sequence

bromide resp. 2-chloromethylthiophene should lead to the desired products **2a-c** and **3a-c**. Unexpectedly, when using $NaNH_2$ for the deprotonation of **1b**, the ring-opened product **12** was isolated instead of **4b**. This result suggested that within the heterogeneous mixture the alkylation occurred at the ring nitrogen via the following tentative mechanism: Deprotonation induced then a retro-Michael reaction leading finally to ring opening of the piperidine core (Scheme 3).[8]



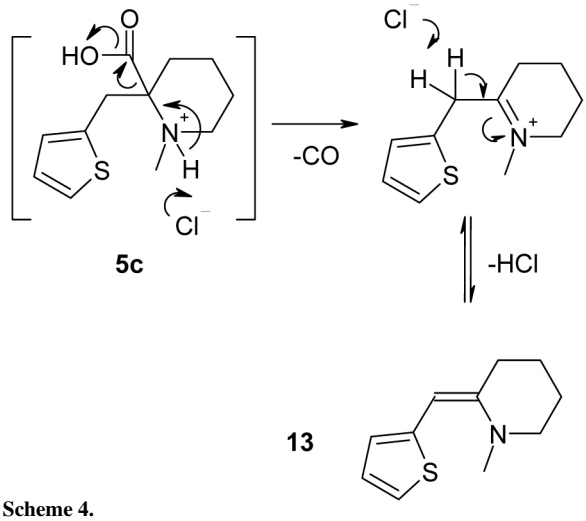
Scheme 3.

When an LDA solution in THF was applied as the base instead of $NaNH_2$ and the temperature was lowered to –5 °C the desired products **2a-c** and **3a-c** were obtained in good yields in all experiments (Scheme 2).

Initially, it was envisaged to cyclize the esters **2a-c** and **3a-c** directly to the corresponding cyclic ketones **6** and **7**. Possible reagents known for similar reactions are e.g. a mixture of methanesulfonic acid and P_2O_5,[9] or PPA,[5a,10] but none of these reagents gave any conversion to the desired products **6** and **7**. Even a previously reported protocol for the cyclization of the corresponding ethyl ester of **2a** to **6a** did not give the desired compound in our hands.[9] Although the cyclization of the corresponding ethyl ester of **2c** to **6c** was reported[11] (37% yield) in the case of the methyl ester **2c** this result could not be verified. As examples for similar cyclizations of esters are relatively rare we decided to undertake further cyclization attempts with the free acids. After hydrolysis with conc. hydrochloric acid the corresponding acids were isolated as hydrochlorides **4a-c** and **5a-c** and after evaporation of volatiles they were used without further purification in the subsequent cyclization.

Initially, cyclization of **4a** was attempted with $MeSO_3H/P_2O_5$[9] starting at room temperature. However, even at 80 °C no satisfactory yield of **6a** was obtained (<10%). A similarly disappointing result was observed in the reaction with $MeSO_3H$ at room temperature and H_2SO_4 at 80 °C. In both cases no product was isolated at all.

Consequently, more forcing cyclization conditions were required as have been published using PPA in similar reactions.[10b] Intermediates **4a-c** and **5a-c** were then reacted in PPA at 130 °C. In the benzo-series (starting materials **4a-c**) the desired products were now isolated in good to excellent yields (Scheme 2) after 14 hours. In the thieno-series (starting materials **5a-c**) PPA had to be replaced by polyphosphoric acid ester (PPE) but only the 3- and 4-N-methyl products **7a** and **7b** were obtained in moderate yields. In the reaction of the 2-N-methylated intermediate **5c** no product **7c** was obtained. Further investigation of this reaction showed that decarbonylation and dehydration of **5c** led to the corresponding enamine **13** (Scheme 4). Examples for similar reactions are the known decarbonylations of α-hydroxycarboxylic acids.[12]

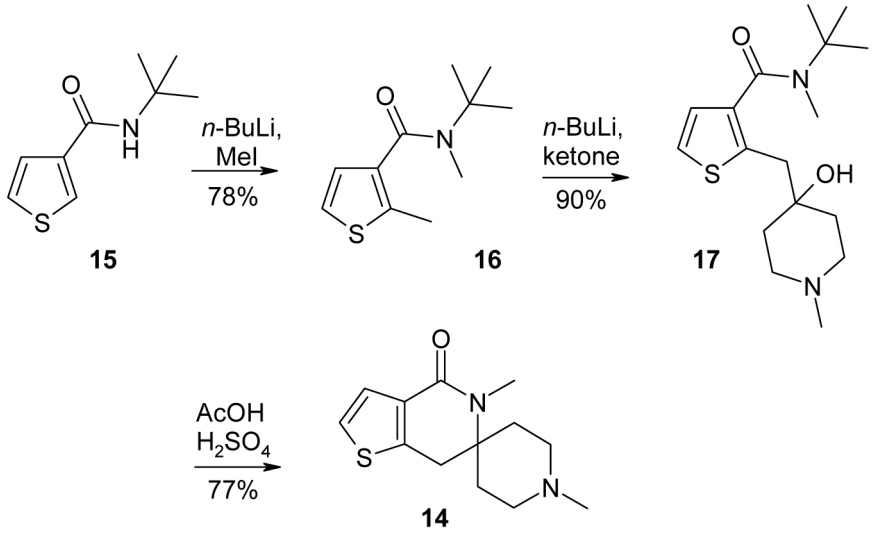


Scheme 4.

The last step in the synthesis towards the target molecules was the ring expansion to spiro-lactams **10** and **11**. For this ring expansion we considered two reaction types: A direct Schmidt reaction or a Beckman rearrangement reaction via an oxime intermediate.

Representing a one-step strategy, the Schmidt reaction was investigated first. Ketone **6a** was dissolved in conc. H_2SO_4 or PPA and sodium azide was added. Nitrogen evolution from the reaction mixture showed that the reaction had started but unfortunately, only decomposition was observed.

The Beckmann rearrangement is a two step process and the oximes **8a,b** and **9a,b** had to be synthesized from the corresponding ketones with hydroxylamine in ethanol and pyridine as base.[13] Tentatively, due to sterical hindrance of the carbonyl group of the ketones this reaction was very slow but after 3 days the oximes were finally obtained in good purity so that they could be further reacted without additional purification. The crude oximes were dissolved directly in PPA and after 2 hours at 130 °C the desired products **10a,b** and **11a,b** were isolated in moderate to good yields (Scheme 2). It has to be mentioned that the Beckmann rearrangement of compounds closely related to **8a,b** (bearing a cyclopentane- or cyclohexane instead of the piperidine ring) have been reported to give the isomeric products, where the NH functionality is connected to the phenyl ring.[14] However, we can not confirm these unusual results as in our experiments only the products **10a,b** resp. **11a,b** were isolated. This was confirmed by synthesizing **14**, the N-methyl derivative of compound **11a** via an alternative route (Scheme 5). Starting from N-(1,1-dimethylethyl)thiophene-3-carboxamide[15] **15** the amide and the 2-position of the thiophene ring were methylated using n-BuLi and MeI to give **16**. Subsequently the methyl-side chain of **16** was again lithiated with n-BuLi and then reacted with N-methyl-piperidin-4-one. The so obtained **17** was finally cyclized to **14** with H_2SO_4 in acetic acid. Comparison of the NMR data of



Scheme 5.

compound **14** and **11a** confirmed the assigned regiochemistry of **11a**.

3. Conclusion

The results presented in this paper show an extension of the product variety of the series of spiranes to the described spiro-lactams. We developed an easy synthetic route to spiro-compounds of type **10** and **11** via successful alkylation of readily available 1-methylpiperidinecarboxylates, cyclization and Beckmann rearrangement of the resulting cyclic ketones via the corresponding oximes. The overall process contains 5 steps, whereas two intermediates, the hydrochlorides **4** and **5** and the oximes **8** and **9**, can be used as crude products thus avoiding elaborate purification. The best yield in the overall sequence was obtained for product **10a** with 55% over 5 steps; **11b** gave the lowest yield of all investigated compounds with 19% over all.

4. Experimental

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. All solvents were distilled prior to use. NMR spectra were recorded from $CDCl_3$ solutions on a Bruker AC 200 (200 MHz) spectrometer and chemical shifts are reported in ppm using TMS as internal standard. Combustion analysis was carried out in the Microanalytic Laboratory of the University of Vienna.

General procedure A: Alkylation of 1-methylpiperidinecarboxylates to compounds 2a-c and 3a-c. To a freshly prepared solution of LDA (1 equiv) in dry THF (5% solution) a solution of the corresponding 1-methylpiperidinecarboxylate **1** (1 equiv) was added in dry THF (5% solution) at –5 °C under nitrogen. After 30 minutes benzyl bromide or 2-thenyl chloride (1 equiv. in dry THF, 10% solution) was added and the reaction mixture was allowed to warm to room temperature. After 2 hours at room temperature the reaction mixture was poured onto water and extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude products were purified by Kugelrohr distillation.

4-Benzyl-1-methylpiperidine-4-carboxylic acid methyl ester (2a). 1-Methylpiperidine-4-carboxylic acid methyl ester **1a** (10.0 g, 63.6 mmol) was converted with benzyl bromide (11.0 g, 64.3 mmol) according to general procedure A to give 12.2 g (49.3 mmol) of **2a** (78%) as colorless liquid after Kugelrohr distillation; bp 100–102 °C/0.3 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.17–6.75 (m, 5H, H2-6), 3.55 (s, 3H, OCH_3), 2.75 (s, 2H, $ArCH_2$), 2.75–2.50 (m, 2H, CH_2), 2.18 (s, 3H, NCH_3), 1.34 (m, 6H, CH_2); ^{13}C NMR (50 MHz) δ: 174.4 (s, CO), 135.9 (s, C1), 129.0 (d, C3/5), 127.1 (d, C2/6), 125.7 (d, C4), 52.3 (t, C2'/6'), 50.2 (q, OCH_3), 45.8 (q, NCH_3), 45.3 (t, CH_2), 32.6 (t, C3'/5').

3-Benzyl-1-methylpiperidine-3-carboxylic acid methyl ester (2b).[16] 1-Methylpiperidine-3-carboxylic acid methyl ester **1b** (8.0 g, 50.9 mmol) was converted with benzyl bromide (8.7 g, 50.9 mmol) according to general procedure A to give 8.0 g (32.3 mmol) of **2b** (64%) as colorless liquid after Kugelrohr distillation; bp 87–94 °C/0.14 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.30–6.90 (m, 5H, H2-6), 3.45 (s, 3H, OCH_3), 2.85 (d, J = 11.5 Hz, 1H, $ArCH_2$), 2.65 (d, J = 11.5 Hz, 1H, $ArCH_2$), 2.55–2.25 (m, 2H), 2.20 (s, 3H, NCH_3), 2.10–1.00 (m, 6H); ^{13}C NMR (50 MHz) δ: 174.6 (s, CO), 136.4 (s, C1), 129.2 (d, C3/5), 127.4 (d, C2/6), 126.0 (d, C4), 62.3 (t, C2'), 55.5 (t, C6'), 50.7 (q, OCH_3), 48.0 (s, C3'), 46.1 (q, NCH_3), 43.2 (t, $ArCH_2$), 30.3 (t, C4'), 22.3 (t, C5'); Anal. Calcd. for $C_{15}H_{21}NO_2$: C 72.84; H 8.56; N 5.66. Found: C 73.03; H 8.64; N 5.53.

2-Benzyl-1-methylpiperidine-2-carboxylic acid ethyl ester (2c). 1-Methylpiperidine-2-carboxylic acid ethyl ester **1c** (10.0 g, 58.4 mmol) was converted with benzyl bromide (10.0 g, 58.5 mmol) according to general procedure A to give 10.6 g (40.6 mmol) of **2c** (69%) as colorless liquid after Kugelrohr distillation; bp 100 °C/0.2 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.20–6.94 (m, 5H, H2-6), 4.12 (q, J = 7.2 Hz, 2H, OCH_2), 3.25 (d, J = 12.9 Hz, 1H, $ArCH_2$), 2.84 (d, J = 12.9 Hz, 1H, $ArCH_2$), 2.77 (s, 3H, NCH_3), 2.72–1.34 (m, 8H, H3'-H6'), 1.25 (t, J = 7.16 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz) δ: 173.1 (s, CO), 136.5 (s, C1), 130.0 (d, C3/5), 127.3 (d, C2/6), 125.8 (d, C4), 65.7 (s, C2'), 59.3 (t, OCH_2), 51.6 (t, C6'), 41.9 (t, $ArCH_2$), 39.1 (q, NCH_3), 32.0 (t, C3'), 24.9 (t, C4'), 20.9 (t, C5'), 13.9 (q, OCH_2CH_3); Anal. Calcd. for $C_{16}H_{23}NO_2$: C 73.53; H 8.87; N 5.36. Found: C 73.25; H 8.94; N 5.23.

1-Methyl-4-(2-thienylmethyl)-piperidine-4-carboxylic acid methyl ester (3a). 1-Methylpiperidine-4-carboxylic acid methyl ester **1a** (12.0 g, 76.3 mmol) was converted with 2-chloromethylthiophene (10.2 g, 76.9 mmol) according to general procedure A to give 12.8 g (50.5 mmol) of **3a** (66%) as colorless liquid after Kugelrohr distillation; bp 83 °C/0.23 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.05 (dd, ^{1}J = 4.3 Hz, ^{2}J = 0.9 Hz, 1H, H5), 6.84 (dd, ^{1}J = 4.3 Hz, ^{2}J = 2.9 Hz, 1H, H4), 6.68 (dd, ^{1}J = 2.9 Hz, ^{2}J = 0.9 Hz, 1H, H3), 3.64 (s, 3H, OCH_3), 3.00 (d, 2H, $ArCH_2$), 2.81–2.43 (m, 2H, CH_2), 2.24 (s, 3H, NCH_3), 2.14–1.34 (m, 6H, CH_2); ^{13}C NMR (50 MHz) δ: 174.5 (s, CO), 137.6 (s, C2), 125.9 (d, C3/4), 123.4 (d, C5), 52.2 (t, C2'/6'), 50.7 (q, OCH_3), 45.6 (q, NCH_3), 45.5 (s, C4'), 39.1 (t, $ArCH_2$), 32.6 (t, C3'/5'); Anal. Calcd. for $C_{14}H_{21}NO_2S$: C 61.63; H 7.56; N 5.53. Found: C 61.77; H 7.65; N 5.77.

1-Methyl-3-(2-thienylmethyl)-piperidine-3-carboxylic acid methyl ester (3b). 1-Methylpiperidine-3-carboxylic acid methyl ester **1b** (5.9 g, 37.5 mmol) was converted with 2-chloromethylthiophene (5.0 g, 37.7 mmol) according to general procedure A to give 6.1 g (24.1 mmol) of **3b** (64%) as colorless liquid after Kugelrohr distillation; bp 61–63 °C/0.03 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.04 (dd, ^{1}J = 5.4 Hz, ^{2}J = 1.3 Hz, 1H, H5), 6.84 (dd, ^{1}J = 5.4 Hz, ^{2}J = 4.0 Hz, 1H, H4), 6.65 (dd, ^{1}J = 4.0 Hz, ^{2}J = 1.3 Hz, 1H, H3), 3.63 (s, 3H, OCH_3), 3.26 (d, J = 14.0 Hz, 1H, $ArCH_2$), 3.04 (d, J = 14.0 Hz, 1H, $ArCH_2$), 2.20 (s, 3H, NCH_3), 2.50–1.20 (m, 8H, CH_2); ^{13}C NMR (50 MHz) δ: 174.9 (s, CO), 138.4 (s, C2), 126.4 (d, C3/4), 123.8 (d, C5), 62.0 (t, C2'), 55.7 (t, C6'), 51.3 (q, OCH_3), 48.2 (s, C3'), 46.3 (q, NCH_3), 36.6 (t, $ArCH_2$), 30.2 (t, C4'), 22.3 (t, C5'); Anal. Calcd. for $C_{14}H_{21}NO_2S$: C 61.63; H 7.56; N 5.53. Found: C 61.67; H 7.64; N 5.75.

1-Methyl-2-(2-thienylmethyl)-piperidine-2-carboxylic acid ethyl ester (3c). 1-Methylpiperidine-2-carboxylic acid ethyl ester **1c** (4.0 g, 23.4 mmol) was converted with 2-chloromethylthiophene (3.1 g, 23.4 mmol) according to general procedure A to give 4.3 g (16.1 mmol) of **3c** (69%) as colorless liquid after Kugelrohr distillation; bp 85 °C/0.3 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.07 (m, 1H, H5), 6.91–6.72 (m, 2H, H3/4), 4.19 (q, J = 5.7 Hz, 2H, OCH_2), 3.32 (d, J = 12.9 Hz, 1H, $ArCH_2$), 3.17 (d, J = 12.9 Hz, 1H, $ArCH_2$), 2.84–2.59 (m, 2H, H6'), 2.46 (s, 3H, NCH_3), 1.82–1.49 (m, 6H, H3'-5'), 1.29 (t, J = 5.7 Hz, 3H, OCH_2CH_3); ^{13}C NMR (50 MHz) δ: 174.9 (s, CO), 138.4 (s, C2), 126.3 (d, C4), 125.0 (d, C5), 123.7 (d, C3), 65.8 (s, C2'), 59.2 (t, OCH_2), 51.6 (t, C6'), 39.0 (t, $ArCH_2$), 35.5 (q, NCH_3), 32.0 (t, C3'), 24.8 (t, C5'), 20.9 (t, C4'), 13.9 (q, OCH_2CH_3); Anal. Calcd. for $C_{14}H_{21}NO_2S$: C 62.89; H 7.92; N 5.24. Found: C 62.90; H 7.99; N 5.29.

General procedure B: Cyclization to 6a-c and 7a,b. A 5% solution of the ester (**2** or **3**) in hydrochloric acid (36%) was stirred under reflux for 15 hours. After cooling to 50 °C, the mixture was evaporated to dryness under reduced pressure. The hydrochloride was then poured into polyphosphoric acid (4% solution of the hydrochloride) at 130 °C and stirred at that temperature for 18 hours. After cooling to 50 °C, the mixture was poured onto ice and a basic pH was adjusted with sodium hydroxide (30% solution in water). This solution was continuously extracted with diethyl ether for 18 hours. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude products were purified by Kugelrohr distillation.

1'-Methylspiro[(2*H*)-indene-2,4'-piperidine]-1(3*H*)-one (6a).[9] 4-Benzyl-1-methylpiperidine-4-carboxylic acid methyl ester **2a** (5.0 g, 20.2 mmol) was converted according to general procedure B to give 3.84 g (17.8 mmol) of **6a** (88%) as colorless liquid after Kugelrohr distillation; bp 110 °C/0.03 mbar (KRD); mp 68–72 °C; ^{1}H NMR (200 MHz) δ: 7.68–7.07 (m, 4H, H4-7), 2.94 (s, 2H, H3), 3.04–2.43 (m, 2H, CH_2), 2.24 (s, 3H, NCH_3), 2.17–1.79 (m, 4H, CH_2), 1.63–1.15 (m, 2H, CH_2); ^{13}C NMR (50 MHz) δ: 209.0 (s, CO), 151.4 (s, C3a), 135.1 (s, C7a), 134.1 (d, C5), 126.7 (d, CH), 123.4 (d, CH), 123.0 (d, CH), 51.8 (t, C2'/6'), 47.4 (s, C4'), 45.8 (q, NCH_3), 38.0 (t, C3), 32.8 (t, C3'/5'); Anal. Calcd. for $C_{14}H_{17}NO$: C 78.10; H 7.96; N 6.51. Found: C 78.04; H 8.08; N 6.36.

1'-Methylspiro[(2*H*)-indene-2,3'-piperidine]-1(3*H*)-one (6b). 3-Benzyl-1-methylpiperidine-3-carboxylic acid methyl ester **2b** (3.6 g, 14.6 mmol) was converted according to general procedure B to give 2.7 g (12.5 mmol) of **6b** (86%) as colorless liquid after Kugelrohr distillation; bp 102–105 °C/0.2 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.81–7.10 (m, 4H, H4-7), 3.30 (d, J = 16.1 Hz, 1H, H3), 3.00 (d, J = 16.1 Hz, 1H, H3), 2.43 (d, J = 13.4 Hz, 1H, H2'), 2.24 (s, 3H, NCH_3), 2.05 (d, J = 13.4 Hz, 1H, H2'), 1.92–1.12 (m, 6H, H4'-6'); ^{13}C NMR (50 MHz) δ: 207.4 (s, CO), 152.4 (s, C3a), 135.1 (s, C7a), 133.9 (d, C5), 126.5 (d), 125.9 (d), 123.3 (d), 61.7 (t, C2'), 54.7 (t, C6'), 50.0 (q, NCH_3), 45.9 (s, C3'), 38.4 (t, C3), 30.2 (t, C4'), 21.9 (t, C5'); Anal. Calcd. for $C_{14}H_{17}NO$: C 78.10; H 7.96; N 6.51. Found: C 77.83; H 8.03; N 6.43.

1'-Methylspiro[(2*H*)-indene-2,2'-piperidine]-1(3*H*)-one (6c).[10] 2-Benzyl-1-methylpiperidine-2-carboxylic acid ethyl ester **2c** (4.8 g, 18.4 mmol) was converted according to general procedure B to give 2.8 g (13.0 mmol) of **6c** (71%) as colorless liquid after Kugelrohr distillation; bp 95–98 °C/0.005 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.74–7.00 (m, 4H, H4-7), 3.22 (d, J = 17.2 Hz, 1H, H3), 2.82 (d, J = 17.2 Hz, 1H, H3), 2.53–2.11 (m, 2H, H6'), 2.05 (s, 3H, NCH_3), 1.95–1.12 (m, 6H, H3'-5'); ^{13}C NMR (50 MHz) δ: 207.1 (s, CO), 151.1 (s, C3a), 135.1 (s, C7a), 134.4 (d, C5), 127.9 (d), 126.7 (d), 123.4 (d), 69.1 (s, C2'), 51.2 (t, C6'), 38.7 (q, NCH_3), 34.3 (t, C3), 28.8 (t, C3'), 24.8 (t, C4'), 20.1 (t, C5'); Anal. Calcd. for $C_{14}H_{17}NO$: C 78.10; H 7.96; N 6.51. Found: C 77.90; H 8.20; N 6.27.

General procedure C: Cyclization to 7a,b. A 5% solution of the ester (**3a,b**) in hydrochloric acid (36%) was stirred under reflux for 15 hours. After cooling to 50 °C, the mixture was evaporated to dryness under reduced pressure. The hydrochloride was then poured into polyphosphoric acid ester (4% solution of the hydrochloride) and heated to 130 °C under stirring for 3 hours. After cooling to 50 °C, the mixture was poured onto ice and a basic pH was adjusted with NaOH (30% solution in water). This solution was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude products were purified by Kugelrohr distillation.

1'-Methylspiro[(5*H*)-cyclopenta[b]thiophene-5,4'-piperidine]-4(6*H*)-one (7a). 1-Methyl-4-(2-thienylmethyl)-piperidine-4-carboxylic acid methyl ester **3a** (2.0 g, 7.9 mmol) was converted according to general procedure C to give 1.13 g (5.1 mmol) of **7a** (65%) as colorless liquid after Kugelrohr distillation; bp 95 °C/0.03 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.28 (d, J = 4.3 Hz, 1H, H4), 7.07 (d, J = 4.3 Hz, 1H, H5), 3.00 (s, 2H, H6), 2.67–2.65 (m, 2H, CH_2), 2.27 (s, 3H, NCH_3), 2.30–1.80 (m, 4H, CH_2), 1.60–1.25 (m, 2H, CH_2); ^{13}C NMR (50 MHz) δ: 200.8 (s, CO), 166.9 (s, C6a), 144.2 (s, C3a), 130.5 (d, C3), 119.6 (d, C2), 54.4 (s, C4'), 52.3 (t, C2'/6'), 46.1 (q, NCH_3), 36.5 (t, C6), 33.4 (t, C3'/5'); Anal. Calcd. for $C_{12}H_{15}NOS$: C 65.12; H 6.83; N 6.33. Found: C 65.13; H 6.84; N 6.32.

1'-Methylspiro[(5*H*)-cyclopenta[b]thiophene-5,3'-piperidine]-4(6*H*)-one (7b). 1-Methyl-3-(2-thienylmethyl) -piperidine-3-carboxylic acid methyl ester **3b** (2.0 g, 7.9 mmol) was converted according to general procedure C to give 1.20 g (5.4 mmol) of **7b** (69%) as colorless liquid after Kugelrohr distillation; bp 88–90 °C/0.02 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.19 (d, J = 4.3 Hz, 1H, H3), 6.98 (d, J = 4.3 Hz, 1H, H2), 3.26 (d, J = 17.2 Hz, 1H, H6), 2.97 (d, J = 17.2 Hz, 1H, H6), 2.47 (d, J = 11.5 Hz, 1H, H2'), 2.15 (d, J = 11.5 Hz, 1H, H2'), 2.24 (s, 3H, NCH_3), 1.89–1.34 (m, 6H, H4'-6'); ^{13}C NMR (50 MHz) δ: 199.7 (s, CO), 168.4 (s, C6a), 143.8 (s, C3a), 130.3 (d, C3), 119.3 (d, C2), 62.1 (t, C2'), 57.1 (t, C6'), 54.9 (s, C3'), 46.2 (q, NCH_3), 36.7 (t, C6), 30.7 (t, C4'), 22.4 (t, C5'); Anal. Calcd. for $C_{12}H_{15}NOS$: C 65.12; H 6.83; N 6.33. Found: C 65.06; H 6.94; N 6.46.

General procedure D: Beckman rearrangement to 10a,b and 11a,b. To the solution of the spiro-ketone (**6** or **7**) in dry ethanol (1 equiv., 10% solution) hydroxylamine hydrochloride (2 equiv.) and dry pyridine (10% the volume of ethanol) were added and stirred for 3 days under reflux. After cooling the mixture to room temperature NaOH (10% solution in water) was added until a precipitate was formed. This precipitate was collected by filtration, washed with water and dried under reduced pressure. These intermediate oximes were added to 130 °C warm PPA and stirred for 2 hours. After cooling to 50 °C, the mixture was poured onto ice and a basic pH was adjusted with NaOH (30% solution in water). This solution was extracted with diethyl ether in the case of **10a** and **11a,b**. Compound **10b** had to be continuously extracted with diethyl ether for 18 hours. The organic layer was then dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude products were purified by recrystallization from a mixture of diisopropyl ether/2-propanol (1:1).

1'-Methylspiro[(4*H*)-isoquinoline-3,4'-piperidine]-1(2*H*)-one (10a). 1'-Methylspiro[(2*H*)indene-2,4'-piperidine]-1(3*H*)-one **6a** (2.5 g, 11.6 mmol) was converted with hydroxylamine hydrochloride (2.0 g, 28.8 mmol) according to general procedure D to give 2.44 g (10.6 mmol) of **10a** (91%) as colorless crystals after recrystallization; mp 166–168 °C; ^{1}H NMR (200 MHz) δ: 7.97–7.80 (m, 1H, H8), 7.46–6.94 (m, 3H, H5-7), 6.96 (bs, 1H, NH), 2.88 (s, 2H, H4), 2.62–2.30 (m, 4H, H2'/6'), 2.24 (s, 3H, NCH_3), 1.73 (t, 4H, H3'/5'); ^{13}C NMR (50 MHz) δ: 162.8 (s, CO), 135.2 (s, C4a), 130.1 (d, C6), 127.1 (s, C6a), 126.3 (d), 125.3 (d), 124.9 (d), 50.7 (s, C4'), 49.5 (t, C2'/6'), 49.2 (q, NCH_3), 36.3 (t, C4), 34.5 (t, C3'/5'); Anal. Calcd. for $C_{14}H_{18}N_2O$: C 73.01; H 7.88; N 12.16. Found: C 72.73; H 7.83; N 11.98.

1'-Methylspiro[(4*H*)-isoquinoline-3,3'-piperidine]-1(2*H*)-one (10b). 1'-Methylspiro[(2*H*)indene-2,3'-piperidine]-1(3*H*)-one **6b** (2.0 g, 9.3 mmol) was converted with hydroxylamine hydrochloride (1.6 g, 23.0 mmol) according to general procedure D to give 1.4 g (6.0 mmol) of **10b** (65%) as colorless crystals after recrystallization; mp 118–120 °C; ^{1}H NMR (200 MHz) δ: 8.31–7.81 (m, 1H, H8), 7.46–7.00 (m, 3H, H5-7), 6.53 (bs, 1H, NH), 2.99 (d, J = 16.1 Hz, 1H, H4), 2.67 (d, J = 16.1 Hz, 1H, H4), 2.54 (d, J = 10.3 Hz, 1H, H2'), 2.21 (s, 3H, NCH_3), 2.12 (d, J = 10.3 Hz, 1H, H2'), 2.01–1.02 (m, 6H, H4'-6'); ^{13}C NMR (50 MHz) δ: 162.8 (s, CO), 135.2 (s, C4a), 130.1 (d, C6), 127.1 (s, C8a), 126.3 (d), 125.3 (d), 124.9 (d), 65.2 (t, C2'), 54.7 (t, C6'), 52.7 (s, C3'), 45.9 (q, NCH_3), 38.4 (t, C4), 34.3 (t, C4'), 21.9 (t, C5').

1'-Methylspiro[piperidine-4',6-(7*H*)-thieno[3,2-c]pyridine]-4(5*H*)-one (11a). 1'-Methylspiro[(5*H*)-cyclopenta [b]thiophene-5,4'-piperidine]-4(6*H*)-one **7a** (1.1 g, 5.0 mmol) was converted with hydroxylamine hydrochloride (0.7 g, 10.1 mmol) according to general procedure D to give 0.59 g (2.5 mmol) of **11a** (50%) as colorless crystals after recrystallization; mp 180–185 °C; ^{1}H NMR (200 MHz) δ: 7.24 (d, J = 5.7 Hz, 1H, H3), 6.96 (d, J = 5.7 Hz, 1H, H2), 6.05 (bs, 1H, NH), 2.90 (s, 2H, H7), 2.50–2.25 (m, 4H, H2'/6'), 2.20 (s, 3H, NCH_3), 1.75–1.65 (m, 4H, H3'/5'); ^{13}C NMR (50 MHz) δ: 161.6 (s, CO), 143.7 (s, C7a), 130.9 (s, C3a), 124.9 (d), 122.4 (d), 52.7 (s, C4'), 50.5 (t, C2'/6'), 45.2 (q, NCH_3), 36.0 (t, C7), 34.2 (t, C3'/5').

1'-Methylspiro[piperidine-3',6-(7*H*)-thieno[3,2-c]pyridine]-4(5*H*)-one (11b). 1'-Methylspiro[(5*H*)-cyclopenta [b]thiophene-5,3'-piperidine]-4(6*H*)-one **7b** (0.8 g, 3.6 mmol) was converted with hydroxylamine hydrochloride (0.5 g, 7.2 mmol) according to general procedure D to give 0.38 g (1.6 mmol) of **11b** (44%) as colorless crystals after recrystallization; mp 180–185 °C; ^{1}H NMR (200 MHz) δ: 7.29 (d, J = 5.4 Hz, 1H, H3), 6.97 (d, J = 5.4 Hz, 1H, H2), 6.18 (bs, 1H, NH), 3.03 (d, J = 14.8 Hz, 1H, H7), 2.74 (d, J = 14.8 Hz, 1H, H7), 2.65–2.40 (m, 2H, H2'), 2.24 (s, 3H, NCH_3), 2.14–1.05 (m, 6H, H4'-6'); ^{13}C NMR (50 MHz) δ: 161.6 (s, CO), 143.9 (s, C7a), 131.3 (s, C3a),

125.6 (d, C3), 122.9 (d, C2), 64.9 (t, C2'), 54.6 (s, C3'), 45.9 (q, NCH_3), 34.2 (t, C4'/C7), 21.2 (t, C5').

5-(*N*-Benzyl-*N*-methylamino)-2-methylene-pentanoic acid methyl ester (12). Starting material **1b** (4.0 g, 25.5 mmol), $NaNH_2$ (1.1 g, 28.2 mmol) and benzyl bromide (4.0 g, 25.5 mmol) were stirred in dry THF at 35 °C over night under nitrogen. The reaction mixture was poured in water and extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by Kugelrohr distillation to give 3.8 g (15.4 mmol) of **12** (60%) as yellow oil. bp 115 °C / 0.3 mbar; ^{1}H NMR (200 MHz) δ: 7.25 (bs, 5H, H2'-6'), 6.08 (s, 1H, $H1_Z$), 5.47 (s, 1H, $H1_E$), 3.70 (s, 3H, OCH_3), 3.47 (s, 2H, $ArCH_2$), 2.51–2.20 (m, 4H, CH_2), 2.14 (s, 3H, NCH_3), 1.89–1.44 (m, 2H, CH_2); ^{13}C NMR (50 MHz) δ: 166.7 (s, CO), 140.1 (s, C2), 138.9 (s, C1'), 127.5 (d), 126.2 (d), 124.0 (t, CH_2), 61.8 (t, $ArCH_2$), 56.2 (t, C5´), 50.9 (q, OCH_3), 41.5 (q, NCH_3), 29.2 (t, CH_2), 25.8 (t, CH_2); Anal. Calcd. for $C_{15}H_{21}NO_2$: C 72.84; H 8.55; N 5.66. Found: C 73.12; H 8.46; N 5.70.

1-Methyl-2-(1-thien-2-yl-methylidene)piperidine (13). Ester **3c** (2.0 g, 7.9 mmol) was stirred under reflux in hydrochloric acid (36%, 200 mL) for 15 hours. After cooling to 50 °C, the solvent was removed under reduced pressure. This hydrochloride was then treated with polyphosphoric acid ester (60 g, obtained from a $CHCl_3$ solution of P_2O_5 and diethyl ether after removal of the solvent) at 130 °C and stirred at that temperature for 3 hours. After cooling to 50 °C, the mixture was poured onto ice and a basic pH was adjusted with NaOH (30% solution in water). This solution was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by Kugelrohr distillation to give 0.8 g (4.1 mmol) of **13** (52%) as yellow oil; bp 80 °C / 0.04 mbar; ^{1}H NMR (200 MHz) δ: 6.97–6.79 (m, 2H, H4/5), 6.67–6.46 (m, 1H, H3), 5.25 (bs, 1H, ThCH=), 2.91 (t, 2H, H6'), 2.70 (s, 3H, NCH_3), 2.59 (t, 2H, H3'), 1.98–1.44 (m, 4H, H4'/5'); ^{13}C NMR (50 MHz) δ: 147.4 (d, C2'), 142.8 (s, C2), 126.4 (d, C5), 122.7 (d, C3), 120.6 (d, C4), 92.6 (d, CH), 52.8 (t, C6'), 39.9 (q, NCH_3), 26.6 (t, CH_2), 24.5 (t, CH_2), 22.5 (t, CH_2).

1',5-Dimethyl-spiro[piperidine-4',6(7H)-thieno[3,2-c]pyridin]-4(5H)-one (14). Compound **17** (100 mg, 0.31 mmol) was dissolved in 5 mL AcOH and 0.5 mL conc. H_2SO_4 were added dropwise. The reaction mixture was refluxed for 2.5 hours, cooled to room temperature and subsequently poured on ice. The aqueous solution was basified with Na_2CO_3 and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was purified by column chromatography on Al_2O_3 (eluent: LP:EtOAc:NEt_3 = 50:10:1) to give 60 mg of **14** (77%, 0.24 mmol) as yellow oil; bp: 145–150 °C / 0.03 mbar (KRD); ^{1}H NMR (200 MHz) δ: 7.23 (d, J = 5.7 Hz 1H, H4), 6.94 (d, J = 5.7 Hz, 1H, H5), 3.14 (s, 3H, $CONCH_3$), 2.78–2.14 (m, 4H), 2.30 (s, 3H, NCH_3), 2.14–1.44 (m, 4H); ^{13}C NMR (50 MHz) δ: 150.8 (s, C4), 138.8 (s, C7a´, 129.8 (s, C3a), 125.3 (d, C3), 122.8 (d, C2), 76.5 (q, $CONCH_3$), 51.2 (s, C4'), 51.2 (t, C2',6``), 46.0 (q, NCH_3), 35.5 (t, C7), 33.2 (t, C3',5').

***N*,2-Dimethyl-*N*-(1,1-dimethylethyl)-thiophen-3-carboxamide (16).** The amide **15** (4.0 g, 21.8 mmol) was dissolved in 70 mL dry THF and cooled to –15 °C under N_2 atmosphere. First n-BuLi (50 mmol, 2.3 equiv, 20 mL of a 2.5M solution in hexane) was added at that temperature followed by MeI (24.0 g, 169 mmol, 7.75 equiv) in 30 mL dry THF after 5 minutes. The reaction mixture was stirred at –15 °C for 30 minutes and subsequently slowly warmed to room temperature. Et_2O was added and the reaction mixture washed with aq. 2N HCl, water and brine. The organic layer was dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was recrystallized from cyclohexane to give 3.6 g (78%, 17.0 mmol) of **16** as colorless crystals; mp: 51–52 °C; ^{1}H NMR (200 MHz) δ: 6.90 (d, J = 9.7 Hz 1H, H4), 6.78 (d, J = 9.7 Hz, 1H, H5), 2.81 (s, 3H, NCH_3), 2.43 (s, 3H, $ThCH_3$), 1.47 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (50 MHz) δ: 168.2 (s, CO), 137.5 (s), 136.2 (s), 126.5 (d, C4), 121.9 (d, C5), 56.2 (s, $\underline{C}(CH_3)_3$), 33.5 (q), 27.6 (q, $C(\underline{C}H_3)_3$), 13.2 (q, $ThCH_3$).

N-(1,1-Dimethylethyl)-2-(4-hydroxy-1-methyl-piperidin-4-yl-methyl)-*N*-methyl-thiophene-3-carboxamide (17). The amide **16** (1.6 g, 7.57 mmol) was dissolved in 70 mL dry THF and cooled to –25 °C under N_2 atmosphere. Then n-BuLi (8.25 mmol, 1.1 equiv, 3.3 mL of a 2.5M solution in hexane) was added and the reaction mixture stirred for 10 minutes at –25 °C before N-methyl-piperidin-4-one (1.4 g, 12.4 mmol, 1.6 equiv) dissolved in 20 mL dry THF was added dropwise. After 30 minutes the reaction solution was warmed to room temperature and poured onto water. The reaction mixture was acidified with 2N HCl and washed twice with diethyl ether. The aqueous layer was then basified with 10% aq. NaOH and again extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated. The crude product was recrystallized from cyclohexane/diisopropyl ether to give 2.2 g (6.8 mmol) of **17** (90%) as colorless crystals; mp: 68–69.5 °C; ^{1}H NMR (200 MHz) δ: 6.97 (d, J = 5.2 Hz, 1H, H4), 6.79 (d, J = 5.2 Hz, 1H, H5), 2.94 (s, 2H, $ThCH_2$), 2.81 (s, 3H, $CONCH_3$), 2.69–2.20 (m, 4H), 2.25 (s, 3H, NCH_3), 1.76–1.50 (m, 4H), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (50 MHz) δ: 168.7 (s, CO), 139.8 (s), 136.8 (s), 125.9 (d), 122.8 (d), 67.1 (s, C4´), 56.4 (s, $\underline{C}(CH_3)_3$), 51.3 (t, C2´&C6´), 45.7 (q, NCH_3), 40.5 (t, $ThCH_2$), 37.2 (t, C3´&C5´), 34.3 (q, $CONCH_3$), 27.4 (q, $C(\underline{C}H_3)_3$).

5. References

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Povzetek

Prezstavljen je kratek in učinkovit pristop k sintezi novih spiro spojin, ki združujejo benzo- in tieno- kondenzirane laktame in piperidin. Različni derivati so bili pripravljeni z alkiliranjem 1-metilpiperidinkarboksilatov, ciklizacijo do spiroketonov in sledečo Beckmannovo premestitvijo do ustreznih oksimov.